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Individual subject approaches to mapping sensory-biased and multiple-demand regions in human frontal cortex

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Sensory modality, widely accepted as a key factor in the functional organization of posterior cortical areas, also shapes the organization of human frontal lobes. 'Deep imaging,' or the practice of collecting a sizable amount of data on individual subjects, offers significant advantages in revealing fine-scale aspects of functional organization of the human brain. Here, we review deep imaging approaches to mapping multiple sensory-biased and multiple-demand regions within human lateral frontal cortex. In addition, we discuss how deep imaging methods can be transferred to large public data sets to further extend functional mapping at the group level. We also review how 'connectome fingerprinting' approaches, combined with deep imaging, can be used to localize fine-grained functional organization in individual subjects using resting-state data. Finally, we summarize current 'best practices' for deep imaging.

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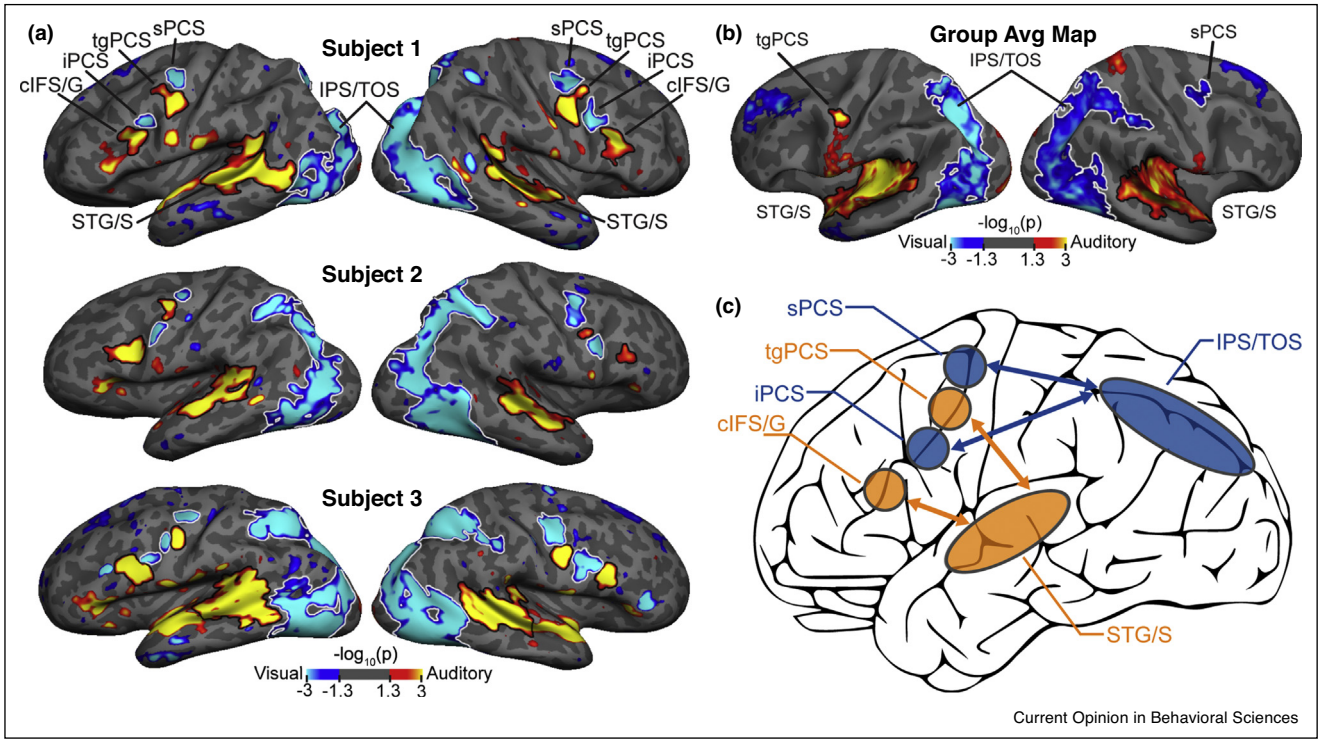
Introduction

The accurate mapping of the functional architecture of the frontal lobes presents a number of scientific challenges. In the human brain, frontal cortex appears to consist of many small functional regions that exhibit substantial anatomical variation across individuals. Recent work has uncovered an increasingly fractionated architecture, with many functionally distinct regions lying within the larger regions defined by early fMRI studies [1,2]. Unlike primary sensory or motor areas, these regions typically exhibit modest levels of functional MRI activation for a variety of cognitive tasks. Because of the low activation levels, frontal lobe researchers traditionally average together the results from many subjects and spatially smooth data in hopes of observing statistically significant activation [3–5]. While that strategy provides advantages in terms of statistical power, it may come at the cost of obscuring fine-scale organization. In particular, small, functionally distinct regions could potentially be obscured and misinterpreted as large functionally homogenous regions. 'Deep imaging,' or the practice of collecting a sizable amount of data on individual subjects, offers significant advantages in revealing fine-scale aspects of functional organization [6•,7••,8–11]. In this paper, we discuss deep imaging approaches to mapping sensory-biased and multiple-demand regions within human lateral frontal cortex.

Sensory-biased frontal lobe regions

Sensory modality preference plays a fundamental role in the functional organization of occipital, temporal, and parietal cortex [12–15]; however, investigations of human frontal lobe have long reported no specificity for sensory modality [4,5,16–19]. This amodal view of human frontal cortex contrasts with substantial non-human primate evidence for strong sensory modality influences in lateral frontal cortex [20,21••,22]. Through the use of deep imaging fMRI methods and fine-scaled within-subject analyses, we have shown across several studies that functional organization of human frontal cortex does indeed exhibit a substantial influence of sensory modality, with multiple visual-biased and auditory-biased regions in lateral frontal cortex. In Ref. [10], we presented subjects with simultaneous streams of multiple visual and multiple auditory stimuli and asked subjects to selectively attend to only a single stimulus stream. The contrast of attend-visual to attend-auditory revealed that the superior branch of the precentral sulcus (sPCS) and the inferior branch of the precentral sulcus (iPCS) were both selectively driven by visual attention (Figure 1). Conversely, the transverse gyrus intersecting the precentral sulcus (tgPCS) and the caudal portion of the inferior frontal sulcus and gyrus (cIFS/G) were both preferentially driven

Figure 1



Comparison of single subject and group averaged analysis of sensory-biased organization. **(a)** Individual subject maps reveal multiple, bilateral visual-biased (blue) and auditory-biased (yellow) regions in human lateral frontal cortex. The visual-biased regions are superior precentral sulcus (sPCS) and inferior precentral sulcus (iPCS). The auditory-biased regions are the transverse gyrus intersecting precentral sulcus (tgPCS) and caudal inferior frontal sulcus (cIFS). In contrast, **(b)** group analysis reveals only a single auditory-biased region in left hemisphere and a single visual-biased region in right hemisphere. **(c)** Schematic of visual-biased (blue) and auditory-biased (orange) regions forming whole brain sensory biased networks across frontal, parietal and temporal lobes. Figures reprinted from [10,44] with permission.

by auditory attention. These interdigitated sensory-biased regions were observed bilaterally and robustly in individual subjects, when the data were examined in native space with no volumetric smoothing and minimal spatial smoothing (3 mm) on the cortical surface (Figure 1a). However, when the data were subjected to group averaging in a common space, the interdigitated pattern of sensory-biased regions was obscured and lost (Figure 1b) — only a single visual-biased region in the right hemisphere and a single auditory-biased region in the left hemisphere persisted. These findings led us to propose a schematic of frontal sensory biased regions and their membership in whole brain networks supporting sensory biased cognition. (Figure 1c) Another functional study identified spatially separate visual-biased and auditory-biased structures in LFC [23], whereas a structural analysis identified complementary connectivity gradients for audition and vision within lateral frontal cortex [24].

The findings of sensory-biased frontal lobe organization [10] were replicated and extended by an fMRI investigation of visual and auditory working memory [11]. Subjects performed a 2-back working memory (WM) task on blocks of visual stimuli (faces) and auditory stimuli (animal sounds). In order to diminish the influence of verbal strategies and to encourage reliance on sensory working memory mechanisms, stimuli within a block were exemplars of a single category (e.g. female faces, cat sounds). The contrast of visual 2-back WM to auditory 2-back WM conditions revealed the same pattern of visual-biased sPCS and iPCS interleaved with auditory-biased tgPCS and cIFS/G as observed in Ref. [10]. The Noyce study examined several of the same subjects of the Michalka attention study approximately two years later and observed a very high spatial correspondence of the location of the individual sensory-biased regions within individual subjects. Within-subject, cross-session replication is a powerful validation method for deep imaging methods.

These sensory-biased frontal regions are small, relative to sensory-biased regions in posterior cortex. Additionally, between-subject frontal lobe anatomical variability appears to be on a similar spatial scale as the size of these areas. For these reasons, group averaging of the interdigitated visual-biased and auditory-biased regions effectively blurred away

the ability to observe them in our data set. The use of similar group averaging methods could account for prior failures to observe both visual-biased and auditory-biased regions in frontal cortex. Collectively, these results demonstrate the power of deep imaging methods for observing fine-scale functional organization in the human brain.

Multiple-demand versus sensory-biased representations

Prior studies, including some that have emphasized within-subject analyses, have reported that lateral frontal cortex contains 'multiple-demand' regions that are recruited by a broad range of cognitive task-demands [4,25–27]. At first glance, the 'sensory-biased' account might be viewed as contradictory to the 'multiple-demand' account of lateral frontal cortical organization. In order to examine the relationship between sensory-biased regions and multiple-demand regions, we [11] scanned subjects who performed 2-back auditory or visual working memory tasks or performed sensory-motor controls with equivalent stimuli and motor responses but no working memory component. A group-average analysis of the contrast of 2-back versus sensory-motor control, combined across sensory modality, revealed bilateral swaths of activation across the regions of lateral frontal cortex (LFC) that contain sensory-biased regions (Figure 2a). In addition, multiple-demand activation was observed in pre-supplementary motor area (preSMA), anterior insula cortex (AIC), and several regions in posterior cortex including superior temporal gyrus/sulcus (STG/S) and intraparietal sulcus (IPS). Within-subject analysis was performed to examine working memory activation in each sensory modality in these ROIs (Figure 2b–f). The posterior cortical auditory-biased and visual-biased regions (pAud, pVis) exhibited antagonistic interactions between the sensory modalities, with modest suppression of activation during working memory (2-back versus control) for the non-preferred modality. In contrast, all frontal areas of interest exhibited some degree of working memory recruitment in both sensory modalities. There was a notable asymmetry between modalities, with auditory-biased regions exhibiting relatively modest activation during visual working memory and visual-biased regions exhibiting more robust activation during auditory working memory. That is, multiple-demand activation is more closely linked with the visual-biased network than with the auditory-biased network in frontal cortex. Despite exhibiting a degree of multiple-demand responsiveness, the visual-biased regions still preferred visual working memory over auditory working memory. In contrast, pre-supplementary motor area (preSMA) and anterior insula (AI) exhibited true multiple-demand behavior, with equal responsiveness to working memory demands in either sensory modality.

Although Ref. [11] clearly demonstrates a close link between the visual-biased networks and multiple-demand processing in frontal cortex, a number of fundamental questions remain. It is possible that multiple-demand regions only partly overlap with frontal visual-biased regions (and also with frontal auditory-biased regions but to a lesser extent). Additionally, frontal lobe organization might exhibit multiple, overlaid dimensions of functionality. Ref. [10] demonstrated that the degree of cross-modal recruitment of sensory-modality biased frontal regions depended strongly on the informational nature of the task. The 'Modality Appropriateness Hypothesis' of perception suggests that the modality best suited for a perceptual task will be more strongly weighted in making multi-sensory judgements [28]. Specifically, the auditory system exhibits high fidelity for temporal information while the visual system excels in coding spatial information; these strengths of each modality complement the weaknesses of the other modality. In Ref. [10], we proposed the 'domain recruitment hypothesis,' that information domain advantages of sensory modalities extend to cross-modal recruitment of working memory networks.

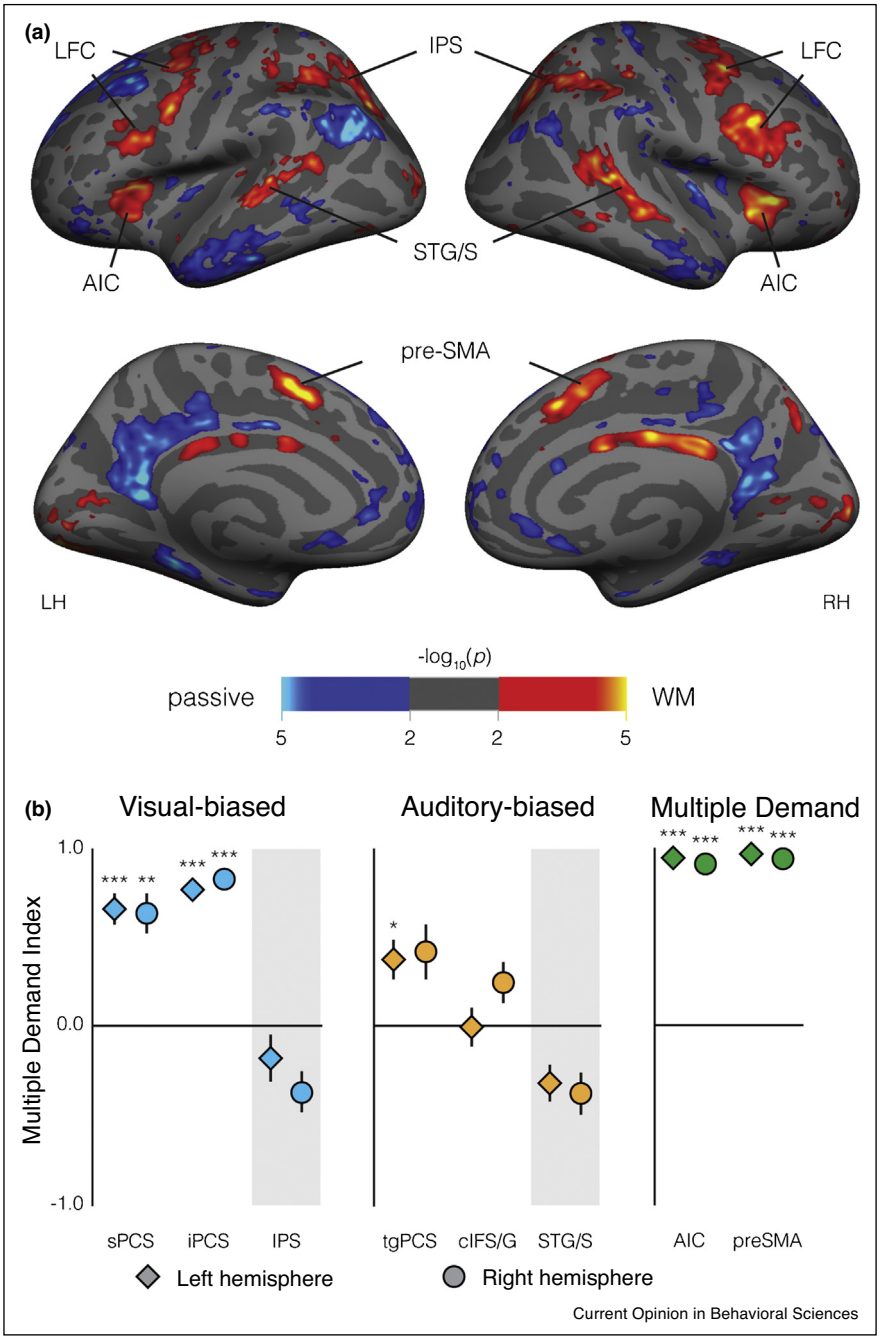
In Ref. [10], a visual WM task that required subjects to remember precise timing of a sequence strongly recruited auditory-biased frontal regions, whereas as a similarly difficult task with only spatial working memory demands did not strongly recruit those areas. Conversely, an auditory WM task with high spatial demands more strongly recruited visual-biased frontal regions than did an auditory temporal WM task with the same stimuli. In Ref. [29], we demonstrated that the domain recruitment extended to visually mapped regions of parietal cortex as well for spatially demanding auditory WM.

Resting-state functional connectivity networks

Resting-state functional MRI (rs-fMRI) scans, in which participants are not given explicit cognitive tasks to perform (other than 'keep your eyes open and let your mind wander'), are effective in revealing brain networks across groups of individuals [2,30–32], but also can reveal fine-scale individual differences in functional organization [6•,7••,33]. We advocate for routinely including rs-fMRI as part of deep imaging protocols. Here, we discuss 3 potential uses: network-level validation in individual subjects, application to large public datasets, and connectome fingerprinting predictions.

In Refs. [10,34,35], we employed task fMRI data to define multiple sensory-biased ROIs in individual subjects, using the approaches described above. These ROIs were then used as 'seed' regions to examine the patterns of resting-state functional connectivity. In Refs. [10,35] seed-to-seed functional connectivity analysis was performed, by averaging the time courses across all voxels or cortical surface vertices within each seed region in each subject and then correlating time courses across possible seed region pairs within a subject (See Figure 3a). This

Figure 2



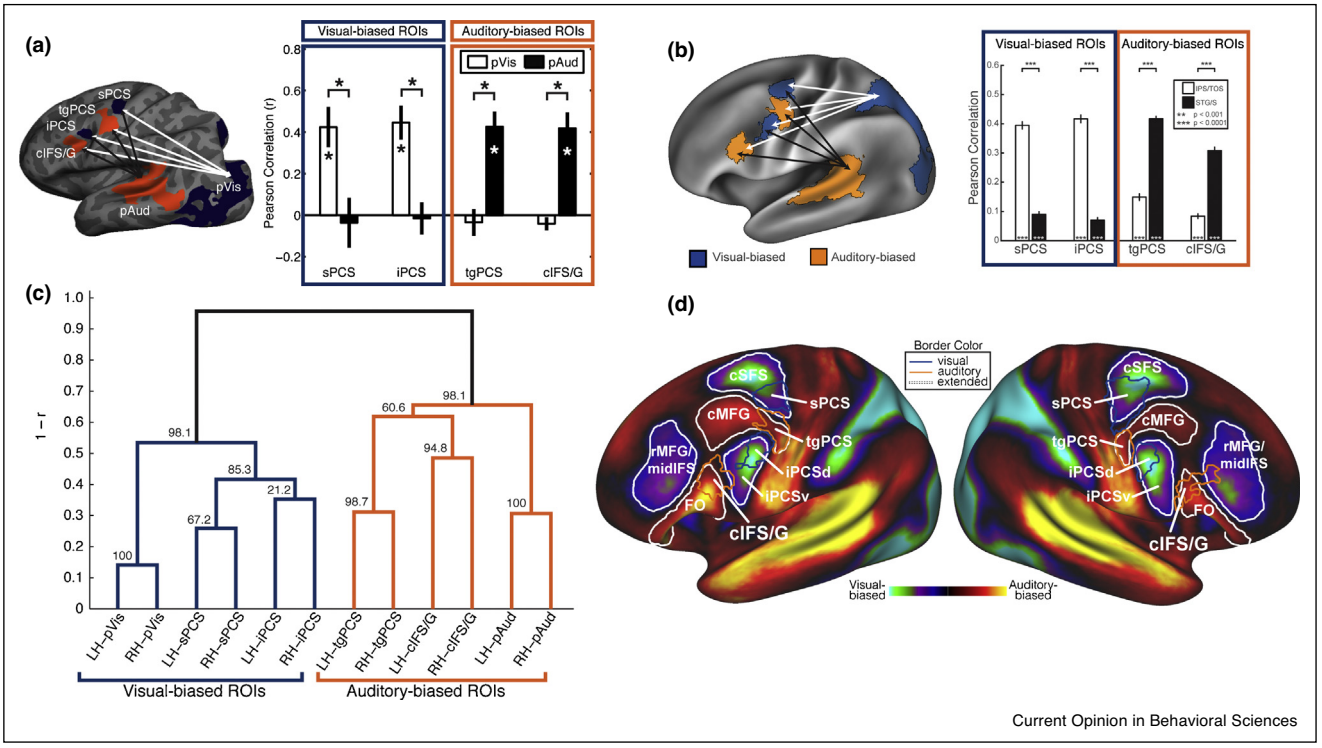
Multiple Demand and Sensory-Biased Regions in Frontal Cortex. **(a)** Group analysis of combined auditory and visual working memory versus sensorimotor control conditions reveals a network of regions activated. **(b)** We characterized each area by computing its Multiple Demand Index (MDI) in each individual subject, using a cosine transform of the ratio between visual and auditory WM responsiveness (each modality's WM versus control; see Noyce *et al.* [11] for details). The Multiple Demand Index ranges between −1 and 1. An MDI score of 1 indicates equal WM activation in each sensory modality; 0 indicates strict selectivity for the preferred modality, and negative numbers reflect competitive interaction between modalities, with activation in the preferred modality and suppression in the non-preferred modality. This analysis reveals that anterior insula cortex (AIC) and pre-supplementary motor area (preSMA) are truly multiple-demand areas responding equally well to working memory in either sensory modality. In contrast, auditory-biased frontal regions tgPCS and cIFS/G reveal low levels of recruitment during visual working memory. sPCS and iPCS exhibit an intermediate degree of multiple-demand activity, exhibiting response for auditory working memory, but stronger responses for visual working memory. Posterior sensory regions (STG/S and IPS) are the most sensory-specific. Figures reprinted from [11] with permission.

analysis revealed that even though frontal regions sPCS, tgPCS, iPCS, and cIFS/G are relatively small and alternate by sensory preference, they exhibit strong selectivity for preferred sensory modality in their connectivity to posterior cortical regions. Visual-biased sPCS and iPCS exhibited strong connectivity with posterior visual cortical regions and negligible connectivity with posterior auditory cortical regions. Conversely, auditory-biased tgPCS and cIFS/G were strongly connected to posterior auditory cortical regions and negligibly connected to posterior visual regions. Seed-to-seed correlations were also combined across subjects and hierarchical clustering analysis was applied to examine reliability in functional network structure. This revealed strong segregation of visual-biased and auditory-biased networks spanning frontal and posterior cortex (Figure 3c). These resting-state functional connectivity analyses therefore provide important confirmation of the task-fMRI findings on sensory-biased frontal cortical organization.

The proliferation of public datasets (e.g. Human Connectome Project – HCP) provides another opportunity to utilize resting-state and task data. Although public data sets are unlikely to contain the specific task contrast examined in in-lab deep imaging investigations, many such data sets do include high-quality resting-state data. In Ref. [36], we created probabilistic ROIs for each frontal and posterior sensory-biased region identified in 9 subjects from Ref. [10] and used those ROIs to examine resting-state data in 469 subjects of the HCP data set [37]. These analyses (Figure 3b) confirmed the network findings of our small in-lab study. Although there was some loss of specificity, as would be expected from applying probabilistic ROIs, the large N afforded by the HCP data set allowed us to observe clear patterns. More generally, this approach of mapping probabilistic ROIs from in-lab deep imaging studies onto rs-fMRI data of large public data sets offers a low-cost means of validating findings across large populations.

In addition to seed-to-seed analyses, seed-to-vertex resting-state connectivity analysis can be performed in order to more broadly examine network connectivity. In Ref. [36], we again applied probabilistic ROIs drawn from a small set of in-lab subjects to HCP resting-state data. We contrasted functional connectivity maps for auditory and visual posterior cortical seeds by taking the difference of

Figure 3



Resting-state functional connectivity analysis. **(a)**,**(c)** Individual Subject ROIs were defined from task contrast (visual WM versus auditory WM) in frontal and posterior cortex. Seed-to-seed functional connectivity analysis confirmed that the interleaved frontal regions formed sensory-specific networks with traditionally identified sensory biased regions in posterior cortex. **(b)**,**(d)** Seed regions defined from individual subjects from deep imaging studies in our lab were used to construct probabilistic ROIs and the probabilistic ROIs were used to examine resting state data from 469 subjects in the Human Connectome Project. This analysis not only confirmed the network analysis from our small N study (b), but also pointed to additional candidate sensory-biased regions (d). Figures reprinted from [10,36] with permission.

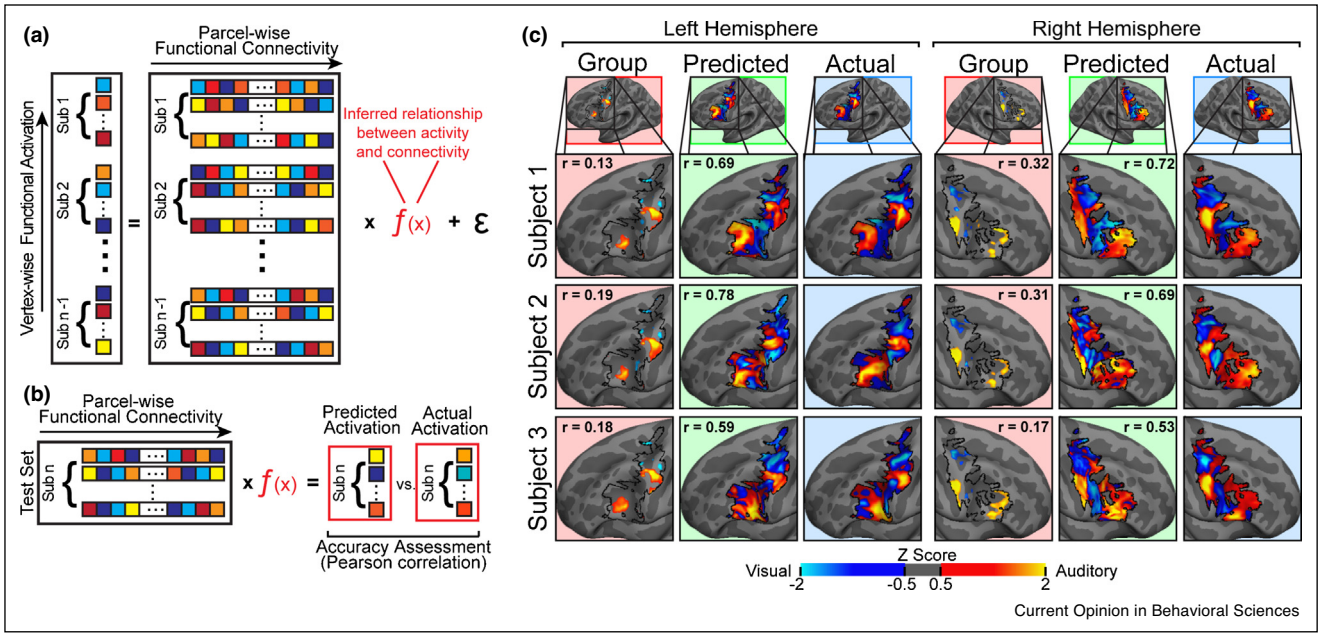
the z-score maps, thresholded to exclude anticorrelation. This analysis (Figure 3d) not only provided a map-based confirmation of the sensory-biased connectivity of sPCS, iPCS, tgPCS, and cIFS/G, but also revealed more anterior sensory-biased candidate regions, including mid-inferior frontal sulcus (midIFS; visual-biased) and frontal operculum (FO; auditory-biased). These maps can then be used to guide further in-lab task-based investigations [35]. Seed-to-vertex maps can also be constructed for in-lab deep imaging data sets [34]. Since the task-defined seeds and the resting-state data come from the same individual subjects, this approach can achieve greater localization specificity than cross-subject applications with out-of-lab datasets. Using this approach, we have revealed functional gradients of organization within parietal cortex [34] and additional visual-biased and auditory-biased regions with frontal cortex [35].

Connectome fingerprinting – connectivity predicts function

The localization of small functional cortical regions in individual subjects presents logistical and financial challenges. Although the deep imaging methods described above and in other articles in this special issue can identify small cortical regions effectively, deep imaging requires collection of a substantial amount of task-fMRI data per subject. This not only places a high price tag on functional localization, in terms of scanner time, but also the prolonged scan sessions required for deep imaging may not be feasible for clinical subjects, children or other subject populations. Connectome Fingerprinting [38–40,41••,42•,43,44], a machine learning approach, can leverage high-quality deep imaging data from one set of subjects to accurately predict functional organization in novel individual subjects from a modest amount of resting-state fMRI data, without the need for deep imaging on these novel subjects.

Passingham *et al.* [41••] proposed that each cortical area has a unique pattern of cortico-cortical connections — a *'connectional fingerprint'* — that could be used to functionally localize cortical areas in individuals. Connectome Fingerprinting (CF) approaches implement this idea in a two-stage process. First, a structure-function CF model of a cortical region (search space) is constructed from connectivity and task data in a population of model-training subjects (Figure 4a). Then for each novel subject connectivity data, the subject's unique *connectome*, is collected and passed through the model to predict the subject's task activation and/or functional organization (Figure 4b,c). High quality individual subject task data, which is obtained in deep imaging studies, is ideal for CF model construction. In addition, high quality connectivity data — either functional

Figure 4



'Connectome Fingerprinting' predicts individual subject functional organization from resting-state data. **(a)** A 'deep imaging' data set consisting of task and resting-state scans on a limited number of subjects can be used to construct a connectivity fingerprint (CF) model of functional organization across a broad region of interest. **(b)** With a CF model in hand, resting-state data only is sufficient to estimate the functional connectome of novel individuals and to then to predict their task activation. **(c)** The connectome fingerprinting approach can yield highly accurate individual subject predictions of task activation that greatly exceed the predictive capabilities of group-level analyses. Figures reprinted from [44] with permission.

connectivity, as obtained from resting-state fMRI [40,43,44] or structural connectivity, as obtained from diffusion tractography [39,42•] — must be collected on the same subjects. Any of several general cortical parcellation schemes (e.g. Refs. [2,31,32]) can be used in the connectivity analysis. CF models relating connectivity and function can be constructed using penalized regression (e.g. ridge) or deep neural network methods. The resulting CF model of a cortical area is simply a series of weights with dimensionality of the parcellation scheme. An individual's task activation within a cortical region can then be predicted by applying the subject's connectome (i.e. connectivity matrix) to the CF model (Figure 4b).

In Ref. [44], we applied CF modeling to two modestly sized (n = 9, n = 14) deep imaging investigations of sensory-biased functional organization in frontal lobes [10,11]. In this analysis, we defined a single lateral frontal cortical search space in each hemisphere (black lines Figure 4c), which was large enough to enclose sPCS, tgPCS, iPCS, and cIFS with high probability. In order to demonstrate the effectiveness of the CF modeling approach in these data sets, we employed a leave-one-subject-out cross-validation procedure, comparing the CF predicted activation with the actual task activation for the left-out subject. CF model predictions (Figure 4c) produced high-fidelity predictions of task activation in individual subjects (spatial correlation of r = 0.67 in RH and r = 0.71 in LH) that greatly outperformed predictions based on group average activity (r = 0.18 in RH and r = 0.22 in LH). In nearly every instance a subject's own connectome produced more accurate task activation predictions than the application of any other subject's connectome, even when that other subject's data was used in construction of the CF model.

CF models of functional organization that are constructed and validated using deep imaging data sets can be released to the public for broader application. In our analysis ~20 min of resting-state data (along with T1 structural scans for standard cortical surface reconstruction [Freesurfer]) yielded high quality predictions of task activity. Even a modest 6 min of resting-state data yielded CF predictions on par with typical cross-task localization methods (e.g. 3 repeats of 4.5 min task runs). The modest scanning requirements of the application of Connectome Fingerprinting models open application to clinical and other populations for whom deep scanning on highly challenging cognitive tasks is not feasible [45,46]. These applications will likely benefit from further advancements in cross-scanner harmonization efforts [38]. Note that a single set of resting-state data can be applied to each of many CF models, constructed for different tasks and/or brain regions to yield a broad set of individual-subject functional localizations. Therefore, there is considerable merit in compiling deep imaging data sets on a broad range of tasks in support of CF models.

Best practices in deep imaging

Deep imaging has the potential to reveal fine-scale functional architecture that can be obscured by group-level analyses. There are notable trade-offs implicit in deep imaging approaches, since investing resources into collecting ample amounts of data per subject implies a potential cost in terms of the number of subjects and/or number of task contrasts studied. We consider four 'best practices' considerations for deep imaging fMRI experiments: Cognitive Task Design; Resting-State fMRI; Research Participants; and Analysis Procedures. Although a number of these factors are helpful across a range of possible experimental objectives, the deep imaging investment in a small number of subjects and possibly a small number of tasks places a high premium on these factors.

Cognitive task design

Since frontal lobe structures might be driven by any of a variety of cognitive factors, it is vital to equate the difficulty of contrasted conditions, if one wishes to draw specific conclusions. Therefore, it is best to pilot test the key conditions in behavioral studies and to fine-tune the experimental design to match performance across conditions. Moreover, since deep imaging methods focus on the analysis of individual research participants, it is critical to produce robust task activation in as many subjects and regions of interest as possible. Therefore, tasks should be highly demanding of cognitive resources, yet within the performance capacity of each individual. We recommend pre-training each participant in the task in a separate behavioral session before the day of scanning. During this training session, the task might initially be presented in an easy format, with the difficulty then ramped up as the subject learns to perform the task. Ideally, subject performance will reach a plateau that is well below 'ceiling' level, before the scan day. The use of multiple tasks within each subject, even if across sessions, also offers a spatial resolution advantage over group studies in examining fine-scale functional organization.

Resting-state fMRI

Resting-state fMRI can be combined with task fMRI data to support investigations of network organization. Application to mining large data sets and to individual subject connectome fingerprinting is described above in detail. Existing resting-state protocols collect anywhere from 6−60 min of data. Although more data is almost always better, there appears to be an inflection point in performance at about 18−20 min of resting-state data [7••,44]. This is a relatively small further investment beyond the task data collection, yet it opens up a number of potential revealing avenues for analysis of functional organization.

Research participants

Given the high investment per subject with deep imaging approaches, there is a premium on the quality of data from each subject. We recommend working with individuals who are both experienced with fMRI scanning, and thus less prone to head movement, and with prolonged performance of cognitive experimental tasks, thus more likely to perform strongly for many repeated task runs. Researchers should be cognizant of the limitations of a smaller sample size for generalization to a broader population and recruit an appropriately diverse group of participants.

Data acquisition and analysis

Deep imaging protocols should acquire high-resolution anatomical images and perform individual subject analyses of fMRI data with minimal to no transformation of the data outside of native space in order to retain high spatial resolution advantages. Cortical analyses are best done in a surface-based pipeline with minimal (e.g. 3 mm) surface-based smoothing and no volume smoothing; subcortical analyses, which require volume-based analysis, will typically benefit from modest smoothing (e.g. 2–3 mm) in the volume. Individual subject ROIs, which are often hand-drawn, can be validated by compared activation patters across or within sessions (e.g. split-half reliability). Probabilistic ROI maps can be constructed from the subject population to characterize the location and anatomical variability of regions.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

David C Somers: Conceptualization, Writing - original draft. **Samantha W Michalka:** Investigation, Writing - review & editing, Visualization. **Sean M Tobyne:** Investigation, Writing - review & editing, Visualization. **Abigail L Noyce:** Investigation, Writing - review & editing, Visualization.

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